

THE TREATMENT OF SEVERE ESSENTIAL HYPERTENSION

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THE most important factor in deciding the type of treatment to be used in any given patient with essential hypertension is the prognosis. The reason for this is that specific hypotensive therapy is difficult to administer, requiring patience and persistence on the part of the physician and patient alike. Such inconvenience does not seem necessary or even desirable in the average case of benign essential hypertension since the life expectancy of such patients usually is good without radical therapy.¹

Thus, a patient who has an ambulatory diastolic blood pressure below 120 mm. of mercury with a further fall during sleep (sedation test) or after several days of rest in bed, and who has normal renal function, good cardiac reserve and grade I or II optic fundi may, on the average, look forward to a normal or nearly normal life span. The symptoms of such a patient should be treated in the same way as one would treat similar symptoms in a normotensive patient; above all, he should be reassured concerning the relatively benign character of his hypertension. Since such patients may carry on a trouble-free existence for many years, it would be foolhardy to attempt to treat them with drugs which have disturbing side effects, with diets that are inconvenient and unpalatable, or with major surgical procedures.

The real problem occurs when the patient with benign hypertension begins to show progression. The patient who has a diastolic pressure consistently above 120 mm. of mercury which does not fall markedly during sleep or with hospital rest and who shows advancing disease as judged by changes in the fundi, kidneys and heart can no longer be treated adequately symptomatically. Some type or types of specific hypotensive therapy are indicated.

In the treatment of the severe case we have resorted to three specific hypotensive procedures: (1) low sodium diets, (2) hypotensive drugs, and (3) surgery. The low sodium diets are two: The Kempner rice diet and the Meade-Johnson low sodium (200 mg.) diet. Drug treatment consists primarily of the extracts of *Veratrum viride* orally administered and

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in certain instances the sympatholytic drugs, principally the dihydrogenated alkaloids of ergot and C-7337. Surgical therapy consists of various types of sympathectomy including the Smithwick lumbodorsal splanchnicectomy and, when cardiac denervation seems desirable, the transthoracic sympathectomy. In addition, excision of pheochromocytoma and repair of a coarctation of the aorta when these rare cases are found and judged operable may be considered curative procedures.

No hypotensive procedure can be depended upon to provide consistent responses in a group of hypertensive patients. Occasional cases will exhibit a dramatic remission following one or another type of therapy or to a combination of these with marked reduction in arterial pressure and regression of many of the other symptoms and signs of their disease. Unfortunately, however, the majority will exhibit slight or insignificant therapeutic responses. Nevertheless, treatment with these procedures, if carried to the point of tolerance, will result in subjective and objective benefit in a significant number of patients with sustained high diastolic blood pressure. Therefore, in this group intensive treatment seems at least worthy of trial.

DIETOTHERAPY

It is still uncertain as to whether the effectiveness of the Kempner rice diet in essential hypertension is due entirely to its low sodium content or whether deficiencies of other substances, especially protein, also may play a role. The rice diet contains about 100 mg. of sodium in the usually consumed daily portion, whereas, the Meade-Johnson low sodium or so-called "Lanolac diet" provides twice this amount of sodium. The evidence that the low sodium content of the rice diet determines its hypotensive action is fairly good since feeding of salt restores the hypertension in both animals² and man.³ The evidence concerning the hypotensive effect of protein restriction is conflicting. In Europe during the war, studies during the siege of Budapest did not indicate any significant hypotensive effect of a diet markedly deficient in protein,⁴ whereas reports from Leningrad indicated that the famine period during the siege resulted in definite amelioration of hypertensive diseases and a marked exacerbation following the lifting of the siege.⁵

Because of this uncertainty in regard to the importance of sodium restriction alone and since the rice diet contains less sodium than any other diet we have made it a practice to begin dietotherapy with a trial of two weeks on the strict Kempner rice diet. If there is improvement in the levels of arterial pressure at the end of this trial period the rice diet, because of its unpalatability, is replaced by the Meade-Johnson 200 mg. sodium diet. However, if at the end of two weeks there is no change in arterial pressure dietotherapy is discontinued. If the diet is rigidly adhered to for more than a month, the flat taste of salt-free food becomes

progressively less distasteful. However, during the first month the temptation to use salt is so great that a check of the urine chloride concentration must be made at weekly intervals even in hospitalized patients. In addition, patients who adhere to the diet usually lose approximately 10 pounds in body weight during the first months of treatment. It is of great value to tell the patient that the diet already permits the maximum amount of sodium and that any "break" in the prescribed regimen, no matter how slight, will destroy its hypotensive effect completely.

A crude but useful method of checking the urine for chloride may be carried out in the office. This is done as follows: To 10 drops of urine in a test tube add 1 drop of 20 per cent potassium chromate solution. The fluid turns yellow. Using the cleaned urine dropper add 2.9 per cent silver nitrate solution drop by drop until there is a distinct color change from yellow to red brown. The number of drops of silver nitrate required to produce the color change approximates the number of grams of chloride per liter of urine.

When a low sodium diet is prescribed for hypertensive patients who have severe renal impairment, repeated checks of the clinical state of the patient as well as the blood nonprotein nitrogen are necessary since in occasional cases the kidneys have lost the ability to conserve body sodium and critical depletion of electrolyte may result. The administration of salt will reverse this process. Similarly, in occasional patients who do not have severe renal disease weakness and lethargy may develop after several weeks or months of sodium restriction. These symptoms are relieved by taking salt but the hypertension will return.

DRUG THERAPY

Compared with the brilliant successes of chemotherapy in other conditions the drug treatment of essential hypertension remains disappointing. In our experience the ester alkaloids of *Veratrum viride*⁶ are the only drugs that have any long-term value in the treatment of severe hypertension. Significant reductions in arterial pressure do not occur uniformly and, as with diet and sympathectomy, in a heterogeneous group of severe hypertensives there are all gradations of response from dramatic hypotensive reactions to no response. Although side effects, particularly nausea and vomiting, are frequent, and collapse reactions are not rare, permanent disability or death has not been reported when the drug is given by the oral route. Therefore, if used with a reasonable amount of care the drug does not seem to be dangerous despite occasional alarming side effects. Profound hypertensive reactions with collapse may be treated by giving 50 mg. of ephedrine intramuscularly and/or 1 mg. of atropine sulfate intravenously.

The recent introduction of well standardized and uniform extracts

such as Anatensol* and Veriloid† † appears to offer some improvement over the crude drug (Vertavis‡) although the latter product is said to be now completely uniform and well standardized. Since the extracts are uniform, dosage may be given safely four times per day (after meals and at bedtime). Such a dosage interval and the use of slow dissolving tablets results in a fairly well sustained hypotensive effect in responsive patients. The present status of the Veratrum alkaloids in the treatment of hypertension has recently been reviewed by Wilkins.⁸

The effective dose in any given patient must be determined by trial. Treatment is begun by administering 1 tablet of Anatensol or Veriloid four times per day (after each meal and at midnight). After forty-eight hours, if there is no fall in arterial pressure, the dosage is increased to 2 tablets per dose and, if necessary, at the end of the next forty-eight hours to 3 tablets, four times per day. In this way dosage is quickly increased to the effective range. The average effective dose has been 8 to 12 tablets per day but has varied widely between 4 and 40 tablets per day. Patients must be seen daily during the initial adjustment period. Our routine is to keep a record of the arterial pressure prior to and three hours after each dose of tablets during the first week or two of treatment. Attempts to regulate dosage in the initial period by checking the patient once or twice per week in the office or clinic are not sufficient.

Some patients will exhibit a satisfactory hypotensive response on such crude adjustment, but the majority will require finer adjustment when the effective dosage range is reached. Thus, it may be that in a given case a dose of 2 tablets is ineffective while 3 tablets produces vomiting. A dose of $2\frac{1}{2}$ tablets, however, will produce significant hypotension without vomiting. Or it may be that the patient consistently will vomit after only one of the doses, e.g., the after-breakfast dose. In such an instance only this dose should be reduced slightly but not the others.

Since cumulation of the drug occurs during continuous administration, the dose usually must be decreased (by half-tablet amounts) after the first weeks or months of treatment, usually because of vomiting. It is of great importance not to reduce the dose too far since the margin between the hypotensive dose and that causing side effects is very slight. Adjustment of dosage of Veratrum parallels in many respects the procedure used in adjusting the dose of belladonna, that is, the dosage is gradually increased until side effects occur and the patient maintained at a dose slightly below that level. In short, the physician who wishes to use Veratrum with any measure of success must work within an extremely narrow dosage range. Since the optimal dose varies widely in different cases it must be determined in each instance by patient and

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persistent trial. It is obvious that such fine adjustment can be carried out most successfully in the hospital, where frequent observations of basal arterial pressure may be used as a guide to dosage.

Because of the chemical similarity between the Veratrum alkaloids and the digitalis glycosides and since Veratrum occasionally may cause arrhythmias such as nodal rhythm, heart block and bigeminal rhythm, it has been suggested that the two drugs may be incompatible in therapeutic dosage.⁹ In actual practice, however, this has seldom been the case. We have given digitalis to patients who are taking Veratrum, and have administered Veratrum to previously digitalized patients without adverse side effects in most cases.

The percentage reduction in arterial pressure, while occasionally dramatic, usually amounts to about 15 to 20 per cent of the mean arterial pressure. Nevertheless, we have seen repeatedly in severe hypertension reductions of 20 to 30 mm. of mercury in diastolic pressure result in the reversal of a progressively malignant process. The primary aim in treatment with this drug is not to reduce the blood pressure to normal, since this is seldom possible, but rather to reduce a dangerously high fixed diastolic pressure to a more benign range. In fact, as stated previously,⁶ Veratrum is most useful in severe hypertension, particularly in malignant hypertension which has not yet proceeded to the uremic stage. In our experience the drug has been more effective in patients, particularly males, with fixed high diastolic pressure than in labile or mild hypertension.

Since there is no known way of determining in advance responsive from nonresponsive patients, an adequate therapeutic trial of Veratrum must be made in each case. As side reactions are so frequent following the drug, the temptation to omit the medication is great, and since the margin between the hypotensive and emetic doses frequently is small, both the physician and the patient may find it less troublesome to fall back on symptomatic treatment. On the contrary, successful therapy even in responsive patients requires a persistent physician and a co-operative patient. It seems apparent, therefore, that the extracts of Veratrum are not drugs for the treatment of mild, asymptomatic hypertension.

SURGICAL AND COMBINED THERAPY

For the average case requiring sympathectomy lumbodorsal splanchnicectomy has become the most generally used procedure. However, there are certain patients who exhibit tachycardia as well as hypertension, the acceleration of heart rate often being most pronounced in the erect position. Following lumbodorsal splanchnicectomy in such cases cardiac acceleration may be very marked and causes considerable discomfort to the patient. In such cases and in others in whom palpitation is a prom-

inent symptom, transthoracic sympathectomy which permits interruption of the sympathetic nerves to the heart seems to be the preferable procedure. Some surgeons prefer the latter operative approach since it permits more ready visualization of the sympathetic chain. However, the operative mortality is said to be slightly higher with this operation than with the lumbodorsal or Smithwick operation.

The effectiveness of combined therapy in severe hypertension may necessitate a revision in the criteria for the choice of candidates for surgical sympathectomy. Cases in the past believed to be too far advanced to be suitable for surgery at present may be benefited when medical therapy is used following operation. Indeed, as judged by our as yet limited experience, the only patients that would be excluded from operation are (1) those with far advanced renal disease verging on uremia and (2) elderly patients whose life expectancy is not sufficiently long to warrant operation. The principal indication for operation in our experience are patients who fail to respond or have lost their response to medical treatment alone.

It is apparent from this brief review of the specific hypotensive treatments available at present that none are simple or easily carried out procedures. Nor is it possible as yet to predict in advance with any great degree of success whether the given patient will respond to any or all of these treatments. For these reasons we have reserved such procedures for the treatment of severe hypertension only (diastolic blood pressure persistently above 120 mm. Hg).

It is true that in many instances of severe diastolic hypertension the long-term results with any of the above mentioned treatments used alone have been only fair. Not infrequently reductions in arterial pressure occur especially after surgical and drug therapy, which do not persist. However, we have also observed that the results of treatment with drugs, diet or sympathectomy are more dramatic, more persistent and effect a greater percentage of patients if these forms of treatment are combined.

A second encouraging factor is that in severe hypertension clinical improvement frequently will occur after only moderate reductions in diastolic pressure. Thus, it is not uncommon to see regression of papilledema, hemorrhages and exudates in the optic fundi and great improvement in cardiac reserve with a reduction of diastolic pressure previously maintained persistently at 140 and above to one maintained between 110 and 130 mm. of mercury. Apparently in many cases of this type it is only necessary to reduce diastolic blood pressure from the severe to the benign range.

The following case histories will serve to illustrate the manner in which the various forms of treatment may be combined in order to revert patients from severe to benign hypertension and to maintain them in the less severe range.

CASE I. *Severe Essential Hypertension In Young Negro Male Treated with Extract of Veratrum Viride and Later with Low Sodium Diet Added.* E. C., a 34 year old Negro taxi driver, came to the hospital because of severe occipital headaches of six months' duration and progressively blurred vision of one month's duration. Physical examination disclosed a blood pressure of 250/150 and grade III optic fundi with large exudates but no papilledema. There was no significant cardiac enlargement. The urine contained a trace of albumin with occasional cells and hyaline casts and concentrated to 1.023. Phenolsulfonphthalein excretion was 15 per cent in twenty-five minutes and 35 per cent at the end of an hour.

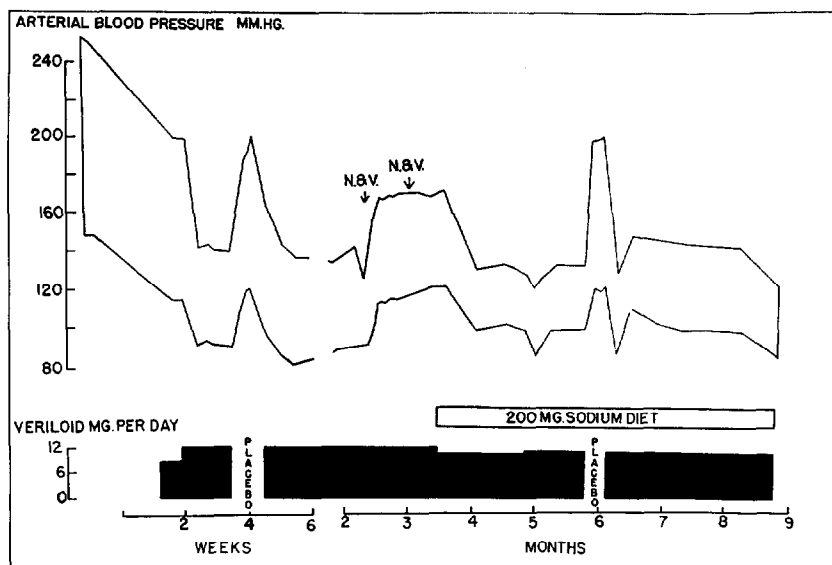


Fig. 228. Chart of arterial pressure and treatment of patient E. C., Negro male, aged 34. Patient discharged from hospital between second and third week of treatment. See text for further details.

After two weeks in the hospital at bed rest, the blood pressure fell to 190/120 (Fig. 228). At this point Veriloid,⁷ an extract of *Veratrum viride*, was given and the dosage increased from 2 mg. four times per day (after meals and at midnight) to 3 mg. four times per day. When the latter dosage was given the blood pressure fell abruptly to 145/90 and remained at this level. After several days the patient was discharged and returned to work, reporting daily for blood pressure measurements. The blood pressure remained reduced despite return to activity. The headaches had disappeared and complete reabsorption of exudates was observed in the fundi.

Without the patient's knowledge a placebo was substituted and within three days the blood pressure had risen to 190/120 and the headache had recurred. On resuming the medication, the arterial pressure again fell to 145/95 and remained at this level for a total of two months. However, at the end of that period he developed several episodes of severe nausea and vomiting requiring slight reduction in dosage and consequent moderate return of arterial pressure to

160/110. Therefore, the 200 mg. Meade-Johnson diet was given in addition, and after two weeks the blood pressure had fallen to 140/95 and has remained approximately at this level for the past five months. When placebo was again substituted for the Veriloid there was partial elevation of the arterial pressure to 195/125 with a prompt fall on resuming medication. Frequent checks of the chloride concentration in the urine indicate that he is maintaining the diet and he has lost 20 pounds in weight. He is entirely asymptomatic, actively employed and has no restrictions on his physical activities. The present dosage of Veriloid is 3, 2, 3 and 3 mg. daily without side effects.

CASE II. Severe Hypertension Treated at First with Veratrum and Diet, Later by Sympathectomy in Addition. A 42 year old former salesman was hospitalized two and a half years ago because of increasing elevation of diastolic blood pressure. Sympathectomy was not done at that time because of impaired renal function and persistent elevation of diastolic pressure at 140 mm. of mercury despite sedation and hospital bed rest. There was a good response to crude *Veratrum viride* (Vertavis) with fall in blood pressure to 180/110. The patient returned to work but after several months the blood pressure rose to 200/120. He then was given the 200 mg. low sodium diet in addition to *Veratrum* but with no further fall in blood pressure. Ten months ago the arterial pressure rose to 230/130 despite Veriloid and low sodium diet and all attempts to increase *Veratrum* resulted in repeated nausea and vomiting. Therefore, a lumbodorsal splanchnicectomy was performed eight months ago. During convalescence from this operation all medical treatment had been discontinued; within a month the patient developed hypertensive encephalopathy with marked elevation of blood pressure to 250/160 mm. of mercury, papilledema, and hemorrhages and exudates in the optic fundi. Salt-free diet and Anatsol (*Veratrum* extract) were begun immediately with good response. At present the patient is asymptomatic, back at work, and the average blood pressure is 180/110 mm. of mercury. The only side effect from Anatsol is occasional vomiting occurring about once per month.

This case is typical of other severe hypertensives in which high levels of diastolic blood pressure returned despite combined drug and diet treatment. Sympathectomy by itself was of less value than medical treatment. However, following operation the patient again responded well to drug and diet therapy.

A similar response has been noted so frequently in patients who have been treated with drugs and diet before and after sympathectomy that we decided to make a special study of this phenomenon. A previous study had indicated that the fall in blood pressure after an intravenous injection of 400 mg. of tetraethylammonium in reactive patients was significantly greater when these patients were taking sodium poor diets than prior to such diets.¹⁰ We have given *Veratrum*, C-7337, and dihydroergocornine both alone and in various combinations. In responsive subjects the combined hypotensive effects of the drugs were additive. It also was apparent that in many cases the hypotensive action of non-toxic doses of *Veratrum viride* extracts was greater after sympathectomy

than before and frequently also was more marked after the low sodium diet than prior to its administration.¹¹

A PROGRAM FOR THE TREATMENT OF MALIGNANT HYPERTENSION

During the past eight months we have treated seven classical cases of the malignant phase of essential hypertension. Two patients who entered the hospital in severe uremia died several days after admission. All of the remaining five patients have shown regression of papilledema and a partial to complete remission of the malignant phase despite the fact that four of these patients have marked impairment of renal function. It is admitted that the period of follow-up has been too brief to pass final judgment on the efficacy of treatment. However, sufficiently impressive short-term results have been obtained to encourage us to publish this regimen of treatment so that it may be evaluated by others.

The patient is hospitalized and given the Kempner rice diet. The blood nonprotein nitrogen and urine chloride concentration are determined every other day to be certain that critical salt depletion does not occur. If the urine chloride concentration does not fall to extremely low levels after a week of such treatment and the nonprotein nitrogen rises, treatment with restricted diets is abandoned.

In addition to dietotherapy the patient is given Anatensol or Veriloid in increasing doses as outlined above until side effects such as nausea and vomiting or severe hypotension occur following which the dosage is reduced to levels slightly below such toxic amounts. In addition, the mixed dihydrogenated alkaloids of ergot (C. C. K. 179) are administered intramuscularly in doses of 0.3 mg. twice per day. Since tolerance develops to sympatholytic agents, after a week Priscoline or C-7337 is given in doses of 50 mg. four times per day by mouth. The following week the dihydrogenated alkaloids of ergot are again substituted and this rotation between Priscoline and these alkaloids continued in order to forestall the development of tolerance.

Definite subjective and objective improvement begins to occur usually within a week or two weeks. As the patient improves he will regain appetite and the 200 mg. low sodium diet is substituted for the Kempner regimen. Treatment with the sympatholytic drugs also may be discontinued at this time. In three of our cases the total duration of hospitalization was only three weeks.

It may be argued that such "shotgun" therapy does not permit the evaluation of any single therapeutic procedure. However, in view of the serious nature of the illness in these patients we did not feel justified in withholding any treatment which might be beneficial. Further, the effectiveness of each of the drugs may be evaluated at any time by substituting a placebo while the contribution of the diet may be estimated by administering enteric coated tablets of sodium chloride.

SUMMARY

The prognosis in stable benign hypertension usually is good, so that only reassurance and symptomatic therapy are required. It is the patient with sustained high diastolic blood pressure who presents the great problem in treatment.

Although no therapy has consistently produced lowering of arterial pressure and clinical improvement, sympathectomy, diets extremely low in sodium, and Veratrum extracts have produced moderate improvement in a certain percentage of severe hypertensives. These various forms of therapy do not provide a satisfactory solution to the problem of treatment in the majority of patients but they are the best of the available procedures and seem worthy of trial in properly selected patients as a means of prolonging their useful lives.

Recent data suggest that by combining these treatments the percentage of good results may be increased appreciably. However, in prescribing a diet, the physician must make certain that sodium is being avoided, while in prescribing the Veratrum alkaloids he must use equal care and persistence in regulating dosage. Provided that the patient is cooperative, such care and persistence not infrequently will be rewarded.

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